expression, FA, and the presence and/or severity of Coronary Artery Disease (CAD).
Methods: Patients, prospectively enrolled, had blood drawn and analyzed for: gene PMs (PCR/RFLP: t-PA, Alu repeat; urokinase, BamHI; PAI-1, HindIII; fibrinogen, HaeIII; MTHFR, HinfI), plasma levels of FPs (ELISA: t-PA, PAI-1, u-PA), fibrinogen (clotting assay), FA (PAP assay), Lp(a) and homocysteine. The absence/presence and severity of CAD was determined by angiographic analyses; medical histories included risk factors. Data were analyzed by logistic regression, multivariate analysis and combined risk factor interactions.
Results: Of the 1107 patients enrolled (57% male, 70% Caucasian, age 19-88 yrs), 465 (21%) had no CAD. Factors associated with CAD presence were: u-PA PM, age, smoking, Lp(a), hypercholesterolemia, PAI-1 activity/antigen and a combined u-PA and fibrinogen PM interaction and gender/age interaction. Factors associated with CAD severity were: u-PA PM, age, smoking, hypercholesterolemia, diabetes, BMI, t-PA antigen, Lp(a) and a combined u-PA and fibrinogen PM interaction, u-PA and t-PA PM interaction, u-PA and MTHFR PM interaction and a gender/race interaction. The u-PA PM, independently and/or in association with other FP PMs, was associated with plasma levels of FA, PAI-1 antigen/activity and fibrinogen, but not u-PA.**Conclusions:** 1) The u-PA PM appears to be associated with the development and progression of CAD; 2) A significant interaction exists between various FP PMs, particularly the u-PA PM, in determining plasma FP levels and FA; 3) Lack of association between the u-PA PM and plasma u-PA levels suggests that regulation of plaque-localized expression of u-PA is important. These results suggest a potential role for FPs/FA and FP gene interactions in the development and progression of CAD with age.

1032-125 Plasma PAI-1 Antigen Concentration Predicts Clinical Outcome of Thrombolytic Treatment of Acute Myocardial Infarction

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Background: Plasminogen activators inhibitor type 1 (PAI-1) is the most important regulatory element in fibrinolytic system, and may be involved in the efficacy of fibrinolytic treatment for acute myocardial infarction (AMI).
Aim: The study aimed to elucidate the association between plasma PAI-1 antigen concentration (PAg) and activity (PAct) before and after standard streptokinase (STK) infusion and clinical outcome in patients (pts) with AMI.
Material and methods: The studied group consisted of 82 pts with AMI with ST elevation (aged 61.0±9.0 yrs, 26 females, 56 males) treated with STK. Plasma PAg and PAct were measured before, immediately after and 1,2,3,4,5 hours after STK infusion using commercially available ELISA tests (Biopool, Sweden). Clinical outcome (mortality, reperfusion and reocclusion rate) was analyzed during mean follow-up of 59 weeks (range 1-96). Kaplan-Meier curves for overall survival (OS) and event-free survival (EFS) were calculated according to PAg concentration.
Results: Peak increase in PAg and PAct was demonstrated after STK treatment in the 3rd hour. Therefore, PAg and PAct at admission to hospital (PAg0, PAct0) and 3 hours after STK (PAg3, PAct3) were further analyzed. PAg3 and PAct3 were significantly higher as compared to PAg0 and PAct0 (30.0±13.3 vs. 20.8±8.6 ng/ml, p=0.001 and 37.3±13.7 vs. 10.0±11.2 IU/ml, p<0.0001, respectively). PAg3 values were increased in pts who died during follow-up (n=15)(40.8±3.3 vs. 24.7±14.2 ng/ml, p=0.038) and in pts without reperfusion (36.5±11.4 vs. 20.3±12.6 ng/ml, p=0.029). Threshold value of PAg3 predictive for no reperfusion, calculated using ROC curve analysis, were 21.8 ng/ml (sens. 77%, spec. 59%, area under the ROC curve 0.65) and for fatal outcome 33.3 ng/ml (sens. 90%, spec. 66%, area under the ROC curve 0.70). The probability of survival of pts with PAg3 over and below 33.3 ng/ml was 65% and 97% respectively (p=0.00016). There was no significant difference in PAct0 and PAct3 between groups separated concerning mortality, reperfusion and reocclusion.
Conclusions: Plasma PAI-1 antigen concentration over 33.3 ng/ml in the 3rd hour after fibrinolytic treatment of AMI predicts unfavorable clinical outcome.

1032-126 Thrombin Potentiates Platelet-Derived Growth Factor Induced Vascular Smooth Muscle Cell Proliferation via PI3 Kinase Activation and p27 Downregulation

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Thrombus formation and vascular smooth muscle cell (VSMC) proliferation are key events in the pathogenesis of vascular diseases. Mediators from both platelets such as PDGF and the coagulation system such as thrombin can affect VSMC proliferation. Thus, we examined whether PDGF and thrombin interact at the level of VSM cell cycle regulation. When human saphenous vein VSMC were stimulated with a maximal concentration of thrombin (3 U/ml), no significant increase in cell number was observed over 4 days. In contrast, thrombin potentiated threshold concentrations of PDGF-BB (1 ng/ml) (increase in cell number: thrombin alone 4'375±2'105; PDGF alone 5'375±2'057; thrombin plus PDGF 18'688±1'711; p=n.s. for thrombin vs. PDGF; p<0.0002 for thrombin or PDGF vs. thrombin plus PDGF; n=4). 3H-thymidine incorporation revealed that potentiation did also occur with ten times lower thrombin concentrations (n=6). Potentiation was prevented by hirudin (3 U/ml). Thrombin did not alter PDGF α or β receptor expression as determined by FACS analysis. Thus, expression of cell cycle proteins regulating G1 progression was determined by Western blotting for up to 30 hours of mitogenic stimulation. The cyclin-dependent kinase inhibitors p21, p27, and p57 were neither affected by thrombin nor PDGF alone. In contrast, thrombin plus PDGF caused p27 downregulation, while p21 was slightly induced, and p57 remained unaffected. Expression of cyclin-dependent kinase 2 (cdk2) and cyclin E was not affected under all these conditions. Cdk2 activity was neither affected by thrombin nor PDGF alone, but enhanced by thrombin plus PDGF. This increase in cdk2 activity was prevented by hirudin. Inhibition of PI3 kinase by LY294002 prevented p27 downregulation in response to thrombin plus PDGF. Thrombin alone did not activate Akt/PKB, while activation by PDGF alone was identical to that by PDGF plus thrombin. Thus, thrombin is not mitogenic for human saphenous vein VSMC, but strongly potentiates VSMC proliferation to PDGF in a dose-dependent manner. This potentiation is related to activation of PI3 kinase, and results in Akt/PKB independent downregulation of the CKI p27.

1032-127 Tissue Factor Pathway in Carotid Atherosclerotic Plaques: Relationships With Clinical Patterns and Risk Factors

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Background: Tissue Factor (TF) and its inhibitor, the tissue factor pathway inhibitor (TFPI) probably play an important role in the thrombogenicity of atherosclerotic plaques but the factors regulating their expression are poorly known.
Methods TF,TFPI and activated factor VII (F VIIa) levels were measured in the atherosclerotic plaques of 100 consecutive patients undergoing carotid endarterectomy. A multiple linear regression model was used to test the relationships between TF, TFPI and FVIIa with 1) documented history of ischemic cerebral events (ICE), 2) conventional cardiovascular risk factors, 3) markers of inflammation (fibrinogen, interleukin-6, CRP) and coagulation activation (thrombin-antithrombin complexes, D-dimers) and metabolic syndrom (Body mass index (BMI), insulinemia, triglyceridemia) and 4) plaque morphology (presence or absence of a massive lipid-rich core).
Results : Plaque TF activity, TFPI antigen and FVIIa were strongly correlated with each other. TF and TFPI but not FVIIa were higher in the 40 symptomatic than in the 60 asymptomatic patients (TF :1.82±0.32 vs 1.02±0.29 mU/gramme of plaque, median± [95%CI]., p=0.008 and TFPI :53.50±11.36 vs 20.60±7.92 pg/g, p=0.0001, respectively). The distribution of traditional cardiovascular risk factors was not different between asymptomatic and symptomatic subjects. TF activity was higher and TFPI was lower in men than in women. The plasma CRP level was a strong independent predictor for plaque TF activity. BMI>25 and massive lipid rich core were positive predictors and hypertriglyceridemia was negative predictors for plaque TFPI.
Conclusion : In carotid plaques, TF and TFPI levels were higher in patients with a documented history of ICE. TF is strongly related to the inflammatory process while TFPI is dependent of the presence of a massive lipid core and of markers of the metabolic syndrom.

1032-128 Novel Role for the Membrane-Bound Chemokine Fractalkine: A Pathophysiologically Relevant Mechanism in Platelet Activation and Adhesion

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Background: Chemokines released by the endothelium have pro-aggregatory properties on platelets. Fractalkine, a recently discovered membrane-bound chemokine with a transmembrane domain, is expressed in vascular injury, however, the effects of fractalkine on platelets have not yet been investigated.
Methods and Results: Blood was taken from healthy Wistar-Kyoto-rats and the expression of the fractalkine-receptor on platelets was demonstrated. The modulation of surface-expression of P-selectin, a reliable marker of platelet activation, was assessed by flow cytometry. P-selectin expression was significantly enhanced by in vitro stimulation with recombinant rat fractalkine (FR: 60.4±7.7 mfu [mean fluorescence units]) as compared with baseline levels (BL: 21.6±2.9 mfu, p<0.001). Preincubation with either the nitric oxide-donor sodium nitroprusside (SNP) or the cyclooxygenase inhibitor acetyl salicylic acid (ASA) prevented the fractalkine-induced increase in surface P-selectin expression. Selectively inhibiting the function of recombinant fractalkine by an antagonizing antibody (anti-FR) or the disruption of the G-protein coupled intracellular signaling cascade of the fractalkine receptor by pertussis toxin (PTX) completely prevented fractalkine mediated platelet activation and adhesion (anti-FR: 15.2±0.9 mfu; PTX: 19.8±3.1 mfu, p<0.001 vs. FR).
In an adhesion flow chamber stimulation with fractalkine significantly enhanced platelet adhesion to collagen and fibrinogen by 20% and 60%, respectively. Similar to P-selectin expression, enhanced adhesion could be prevented by the antagonizing antibody or preincubation of platelets with PTX.
Conclusion: The membrane-bound chemokine induces platelet activation and adhesion. As fractalkine is overexpressed in atherosclerosis and vascular injury it is likely to substantially contribute to increased thrombogenesis in vascular diseases.

1032-129 Mineralocorticoid Receptor Antagonism Attenuates Thrombotic Response to Injury in Atherosclerosis Through Favorable Effects on Nitric Oxide Bioavailability

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Background: Recent studies have demonstrated favorable effects of mineralocorticoid receptor (MR) blockade in conditions associated with up-regulation of the renin-angiotensin axis. We hypothesized that spironolactone modulates thrombotic response to injury in a genetic model of hyperlipidemia.
Methods: LDL receptor knock out mice ($LDLR^{-/-}$) were implanted with spironolactone (35 mg/kg/day) or placebo pellets at 6 weeks while on high lipid chow (5-8 animals/group). At 18 weeks, vasomotor responses were assessed in aortas, with measurement of time to thrombosis after photochemical carotid artery injury. Aldosterone infused animals served